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| 09/979,518 | 04/10/2002 | Judith E Meis | 310307.90134 | 6310 |

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| EXAMINER | |
|---|---|
| HUTSON, RICHARD G | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/979,518 | MEIS, JUDITH E | |
| | Examiner | Art Unit | |
| | Richard G. Hutson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *60,61,63,64,66 and 67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60,61,63,64,66,67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/1/2010 has been entered.

Applicant's amendment of claims 60, 61, in the paper of 3/1/2010, is acknowledged. Applicants filing of the declaration under 37 CFR 1.132/1.132 are acknowledged. Claims 60, 61, 63, 64, 66 and 67 are present and at issue for examination.

Applicants' arguments filed on 3/1/2010, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### *Specification*

The amendment filed on 3/1/2010 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants

recitation of "A Bst strain (ATCC catalog number 12016)..." on page 12 of applicants specification is considered new matter.

Applicants statement that "The specification was amended to clarify that the *Bst* strains useful in the present application include ATCC number 12980 and 12016, both obtained from the American Type Culture Collection, in Rockville, Maryland. This amendment is merely a correction and clarification of the proper ATCC numbers of *Bst* strains useful in the present invention" is acknowledged, however, this statement is not helpful in the determination of where in applicants filed specification support for ATCC number 12016 can be found. The examiner has reviewed applicant's specification but cannot find support for this amendment. Thus it is considered new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60, 61, 63, 64, 66 and 67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 60, 61, 63, 64, 66 and 67 are rejected under this statute, because the recitation and reference to ATCC strain # 12016…" is considered new matter (See also above objection to applicant's specification).

As discussed above, applicants statement that

> "The specification was amended to clarify that the *Bst* strains useful in the present application include ATCC number 12980 and 12016, both obtained from the American Type Culture Collection, in Rockville, Maryland. This amendment is merely a correction and clarification of the proper ATCC numbers of *Bst* strains useful in the present invention."

is acknowledged, however, this statement is not helpful in the determination of where in applicants filed specification support for ATCC number 12016 can be found. The examiner has reviewed applicant's specification but cannot find support for this amendment. Thus it is considered new matter.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 60, 61, 63, 64, 66 and 67 are rejected under 35 U.S.C. 102(a) as being anticipated by Roche Molecular Biochemicals Catalog, 1999, pages 50-51, See IDS.

As previously stated in previous office actions and below, Roche Molecular Biochemicals Catalog, 1999 teaches a one step RT-PCR System and methodologies

comprising incubating RNA templates in a buffer solution containing dNTPs and one or more primers complementary to at least a portion of one or more of the RNA templates with a purified DNA polymerase from *Carboxydothermus hydrogenoformans* and a *Taq* DNA polymerase, in the presence of 12.5 mM Mg and in the substantial absence of Manganese. Roche Molecular Biochemicals Catalog, 1999 further teach that while other thermoactive DNA polymerase with reverse transcriptase activity use manganese ions as co-factors, manganese has a negative effect on the fidelity of DNA synthesis.

It is noted that the method taught by Roche comprises the use of a purified DNA polymerase from *Carboxydothermus hydrogenoformans* and a *Taq* DNA polymerase, both of which comprise a purified polypeptide that exhibits an amino acid sequence exhibited by a full-length DNA polymerase from a Bacillus stearothermophilus (Bst) strain selected from the group consisting of ATCC strain # 12016 and ATCC strain #12980 or a subtilisin digestion product thereof. Each of the polymerases taught by Roche, from *Carboxydothermus hydrogenoformans* and a *Taq* DNA polymerase exhibit many amino acid sequences exhibited by a full-length DNA polymerase from a Bacillus stearothermophilus (Bst) strain selected from the group consisting of ATCC strain # 12016 and ATCC strain #12980. For example, Riggs et al. (Biochemica et Biophysica Acta 1307 (2), pp 178-186 (1996) teach a comparison between Taq polymerase and Bst DNA polymerase (p 183) and show that one such sequence is “YEADD”.

Thus claims 60, 61, 63, 64, 66 and 67 are anticipated by Roche Molecular Biochemicals Catalog.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 60, 61, 63, 64, 66 and 67 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Roche Molecular Biochemicals Catalog, 1999, pages 50-51, (See IDS), Sellman et al. (Journal of Bacteriology, Vol 174, No. 13, pages 4350-4355, see IDS, July 1992) and Lu et al., (BioFeedback, Vol 11, No. 4, pages 464-466, 1991, See IDS).

This rejection was stated in the previous office action as it applied to previous claims 60, 61, 63, 64, 66 and 67. In response to this rejection, applicants have amended claims 60 and 61 filed a declaration under 37 CFR 1.132/1.132 and traverse the rejection as it applies to the claims.

As previously stated, Roche Molecular Biochemicals Catalog, 1999 teaches a one step RT-PCR System and methodologies comprising incubating RNA templates in a buffer solution containing dNTPs and one or more primers complementary to at least a portion of one or more of the RNA templates with a purified DNA polymerase from *Carboxydothermus hydrogenoformans* and a *Taq* DNA polymerase, in the presence of 12.5 mM Mg and in the substantial absence of Manganese. Roche Molecular Biochemicals Catalog, 1999 further teach that while other thermoactive DNA

polymerase with reverse transcriptase activity use manganese ions as co-factors, manganese has a negative effect on the fidelity of DNA synthesis.

Sellman et al. teach the purification and characterization of DNA polymerase from various species of *Bacillus*. Spellman et al. specifically teach the DNA polymerase enzymes from *Bacillus Stearothermophilus* require $Mg^{2+}$ for optimal activity (See abstract). Sellman et al. also teach that the Bst DNA polymerase had its greatest activity at a concentration of magnesium of 10mM and that the addition of more magnesium did not result in a significant increase in polymerase activity.

Lu et al. teach that subtilisin digestion of the Bst polymerase I holoenzyme results in a large fragment that results in the same uniform DNA synthesis as the original full-length enzyme and that this fragment is stable at ambient temperature.

One of skill in the art at the time of the invention would have been motivated to practice methods similar to those taught by the Roche Molecular Biochemicals Catalog, 1999, with the exception of replacing the purified DNA polymerase from *Carboxydothermus hydrogenoformans* and *Taq* DNA polymerase with the DNA polymerase from *Bacillus stearothermophilus* as taught by either Sellman et al. or Lu et al. in order to convert a RNA template to a cDNA template and amplify the synthesized cDNA via a polymerase chain reaction. The expectation of success is high based upon the similar methods taught by Sellman et al. and those taught by Lu et al. who teach similar DNA synthetic reactions using Bst DNA polymerase. It is noted that a part of the motivation to bring together the Bst DNA pol of Sellman et al. with the method of Roche Molecular Biochemicals is based upon the common teaching of the use of magnesium.

That is Roche teaches the use of magnesium as opposed to manganese for an increase in fidelity and Sellman et al. teaches that magnesium provided the optimum activity of the Bst DNA Polymerase. Further given the results of Sellman et al. and Lu et al. and Roche Molecular Biochemicals Catalog, 1999, the substitution of the Bst DNA polymerases taught by Sellman et al. or Lu et al. into the methods taught by Roche Molecular Biochemicals Catalog, 1999 would yield predictable results.

Thus claims 60, 61, 63, 64, 66 and 67 are obvious over Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al.

Applicants continue to traverse this rejection on much of the same basis that applicants have previously traversed.

Applicants submit a Declaration under 37 CFR 1.131/1.132 by Dr Gary Dahl in support of applicant's position that the expectation that the Bst DNA polymerase of Sellman et al. or Lu et al. had reverse transcriptase activity in the absence of manganese is not high or predictable. It is noted that the Bst DNA polymerase from New England Biolabs tested by applicants did not show the presence of a cDNA Band synthesized in the presence of only magnesium. Applicants thus submit that the presence of this required magnesium dependent RT activity is not predictable.

Applicants further submit that they have amended the claims to the use of only those DNA polymerases from particular strains which the Applicants identified as having the claimed activity.

Applicants further point out that the 1999/2000 EPICENTRE Catalog discloses that the Bst DNA polymerase large fragment listed has thermostable RNA-dependent

activity and shows the product provided a 10X Reaction buffer that contained MgCl2, but did not provide any source of Mn2+ cations.

Applicants amendment of the claims and applicants complete argument and statements in the Declaration by Dr Gary Dahl are acknowledged and have been carefully considered, however, are not found persuasive for the reasons previously stated and for those reasons repeated herein.

With respect to the Declaration under 37 CFR 1.131/1.132 by Dr Gary Dahl in support of applicant's position, it is understood that not all DNA polymerases have RT activity in the presence of Mg2+ and in the substantial absence of Mn2+. With this being said, it is not unreasonable that one of skill in the art would want to test the DNA polymerases of Sellman et al. or Lu et al. to see if they have reverse transcriptase activity under the conditions of Roche Molecular Biochemicals catalog, given the teaching of the reduction in fidelity in the presence of manganese. As per KSR, this at least meets the "obvious to try" standard, See *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007).

Further applicants attention is directed to applicants newly amended claims which now are drawn to those methods "comprising incubating" the listed components "under conditions wherein cDNA molecules complementary to one or more of the RNA templates are synthesized". Thus the claimed method, while being drawn to a method of synthesizing cDNA molecules from a RNA template, does not necessarily require such. Thus the standard for success is not as high as applicants appear to argue.

With regard that the expectation is not high or predictable that the Bst DNA polymerase of Sellman et al. or Lu et al. had reverse transcriptase activity in the absence of manganese, based upon the results of applicants as presented in the declaration submitted by Dr Gary Dahl, it is noted that applicants results are for the given Bst DNA polymerase from New England Biolabs under applicants test conditions. It is interesting that applicants submit that the 1999/2000 EPICENTRE Catalog discloses a Bst DNA polymerase large fragment which has thermostable RNA-dependent activity and shows the product provided a 10X Reaction buffer that contained MgCl2, but did not provide any source of Mn2+ cations. It is noted that applicants have stated that they attached a copy of this catalog disclosure as an appendix, however, no such appendix was found in applicant's response. It is noted however, that applicants supply in an earlier IDS a copy of a 1994 EPICENTER Catalog that also would appear to list a Bst DNA polymerase and a buffer containing only magnesium, not manganese. This submission by applicants would not appear to support applicants conclusion that one would not expect Bst DNA polymerase to have RT activity in the absence of manganese, but rather it would appear to support that some Bst DNA polymerase have such activity and some do not, and thus would it not be obvious to try and test for such at the very minimum, especially in light of the teachings of Roche and Sellman et al. regarding the effect of magnesium .

Applicants are requested to supply a copy of the above 1999/2000 EPICENTER Catalog listing the Bst DNA Polymerase Large fragment to which applicants refer but have not supplied.

Applicants noting of similar claims in other U.S. Patents is acknowledged, however, the examiner notes that these are different patents with different issues, and not related to the instant application and do not have a bearing on the instant prosecution.

Thus the combination of the teachings of Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al. provides the motivation to practice similar methods with similar reaction conditions for the two magnesium dependent DNA polymerases, especially with regard to the presence of magnesium and the absence of manganese.

Thus, claims 60, 61, 63, 64, 66 and 67 remain obvious over Roche Molecular Biochemicals Catalog, 1999, Sellman et al. and Lu et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mondesi Robert can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
9/29/2010

/Richard G Hutson/
Primary Examiner, Art Unit 1652